In the Claims:

Claim 20 (amended):

A method of identifying ligands that modulate a *Drosophila* membrane sodium channel, which comprises:

(a) co-expressing an isolated *Drosophila para* voltage-activated sodium channel and an isolated Drosophila voltage activated putative beta subunit, *tipE*, in a host cell selected from the group consisting of *Xenopus* oocytes and a cell from a multicellular organism, wherein the host cell expresses a voltage-activated sodium current[.];

(b) contacting the host cell with a ligand; [and]

(c) measuring the resulting voltage-activated current; and

(d) comparing the voltage-activated current measured according to step (c) with voltage-activated current measured upon contacting said ligand with a control host cell in which said *para* and said *tipE* are not co-expressed.

Remarks:

The claims in this application are 20-26. In an Office Action issued in the parent to the instant CPA on October 28, 1997, claims 20-26 were rejected. However, in the outstanding Office Action, the Examiner acknowledged that claims 24-26 are free of the prior art.

I. 35 U.S.C. 112, Second Paragraph:

Claims 20-26 were rejected as being indefinite.

A. Claim 20 is said to be indefinite because it is said to be unclear whether the cell in which the *para* and *tipE* are expressed lack a voltage-activated sodium channel prior

to the induction of co-expression of the *para* and *tipE* gene products, and if so, it is queried which cells lack a voltage-activated sodium channel.

In response, it is respectfully urged that the method recited according to claim 20 as amended compares the voltage-activated current from a cell in which an isolated *para* and an isolated *tipE* are co-expressed with the voltage-activated current from a control cell in which an isolated *para* and an isolated *tipE* are not co-expressed. In this way, it is not critical whether the host cell itself expresses any basal level of voltage-activated sodium channel activity prior to the induction of expression of the isolated *para* and *tipE* gene products, as it is the *difference* in absolute voltage induced that is relevant. In addition, cells in which such activity is absent are known in the art, may be determined by those having ordinary skill in the art without having to unduly experiment, and are disclosed in the instant specification (see, for example, the disclosure at page 30, lines 9-26). Reconsideration and withdrawal of this ground for rejection therefore respectfully requested.

B. Claims 20-26 are rejected because it is stated that it is unclear what the term *para* means. The Examiner has suggested that the claims would read more clearly if the claim identified *para* as a temperature sensitive mutant paralytic mutation of sodium channels in *Drosophila*.

In order to respond to this ground for rejection and the Examiner's suggestion, claim 20 is hereby amended to recite a definition of *para* found in the specification at page 4, lines 27-30. Having thus amended claim 20, it is respectfully urged that claims 21-26 which depend therefrom are clear and definite. Reconsideration and withdrawal of this ground for rejection is respectfully requested.

C. Claims 20-26 are rejected because it is stated that it is unclear what the term *tipE* means. The Examiner has suggested that the claims would read more clearly if the claim identified *tipE* as a temperature sensitive mutant paralytic mutation of sodium channel in *Drosophila*.

In order to respond to this ground for rejection and the Examiner's suggestion, claim 20 is hereby amended to recite a definition of *tipE* found in the specification at page 4, lines 27-30. Having thus amended claim 20, it is respectfully urged that claims 21-26 which depend therefrom are clear and definite. Reconsideration and withdrawal of this ground for rejection is respectfully requested.

D. Claim 22 is rejected as being unclear because the term "are introduced into the host cell" is said to be unclear. The Examiner queried whether the term encompasses injection of isolated DNA molecules encoding *para* and *tipE* genes into the cells and transfection of vectors which comprise *para* and *tipE* genes. It was also queried whether the *para* and *tipE* genes must be in the same vector, or if two vectors may be used, one comprising the *para* gene and the other encoding the *tipE* gene.

In response, it is noted that the specification broadly teaches introduction of the relevant genes into host cells, and therefore, the language "are introduced into the host cell" is to be read broadly. Thus, at page 9, lines 3-9, it is taught that the *para* and *tipE* cDNAs "may be recombinantly expressed by molecular cloning into an expression vector containing a suitable promoter...", indicating that the *para* and *tipE* genes may both be cloned into a single vector. At page 10, line 30 to page 11, line 13, various methods of introducing the genes into host cells are taught, including transformation, transfection, protoplast fusion, lipofection, and electroporation. At page 11, lines 6-13, microinjection of mRNA is taught. At page 11, lines 30-31, it

is disclosed that voltage-activated sodium channel activity and levels of protein expression "can be determined following the introduction, both singly and in combination, of these constructs into appropriate host cells," thus indicating that the genes do not have to be on the same vector. Accordingly, in view of this broad teaching, it is respectfully urged that the claims are not unclear. Rather, the claims are commensurate in scope with the broad teachings of the methods of introducing these genes into host cells for expression. In view of these remarks, it is not believed that amendment of the claims is necessary in order to overcome the stated ground for rejection. Reconsideration and withdrawal of this ground for rejection is respectfully.

II. 35 U.S.C.103:

Claim 20 stands rejected as being unpatentable over Jackson et al., (D) in view of O'Dowd et al. (J).

A. It is stated that Jackson et al. teach double *Drosophila* mutants expressing *para(ts-1)* and *tipE*. It is then stated:

"Thus cells isolated from these double mutants express para and tipE and are from a multicellular organism."

It is respectfully urged that this statement, which is fundamental to much of the remaining discussion of the prior art found in the outstanding Office Action, is addressed and overcome by the claims as herein amended. Jackson et al., disclose *Drosophila* strains in which the *para* and *tipE* genes are mutated, i.e. by genetic crosses of appropriately mutated parent strains. By contrast, the instant invention and

claims are directed to host cells in which isolated *tipE* and *para* genes have been introduced as isolated genes for co-expression. This distinction is emphasized by including in the claims the term "isolated" in connection with each gene. Accordingly, it is respectfully urged that Jackson et al., neither disclose nor suggest cells from a multicellular organism which co-express isolated *para* and *tipE* genes. In view of this distinction, it is respectfully urged that O'Dowd does not cure the absence of a teaching of isolated *para* and *tipE* gene co-expression. Accordingly, in combination, the Jackson et al. and O'Dowd et al. references neither disclose nor suggest the claimed method for identifying *Drosophila* membrane sodium channel modulatory ligands. Accordingly, a valid *prima facie* case of unpatentability does not exist with respect to the claims as herein amended. Reconsideration and withdrawal of this ground for rejection is respectfully requested.

B. Claims 20-23 stand rejected as being unpatentable over MacKinnon et al (UU) in view of Jackson et al., Loughney et al. (M), and Hall et al. (H).

It is stated that MacKinnon et al. teach a method of identifying ligands that modulate *Drosophila* membrane sodium channel which comprises expressing RNA or cDNA of wild-type or Shaker mutants by injecting the RNA or DNA into *Xenopus* oocytes and measuring the ability of ligands such as charbodotoxin to modulate voltage-activated current in cells injected with RNA or cDNA encoding wild type or mutant sodium channel proteins. It is acknowledged in the outstanding Office Action that MacKinnon et al. do not teach the injection into *Xenopus* oocytes of RNA or cDNA that encodes the *para* and *tipE* genes. Jackson et al. is relied on as a curative teaching.

As noted above, Jackson et al. does not teach the injection of isolated *tipE* or *para* genes to create double mutants. As neither Jackson et al. nor MacKinnon teach isolated *tipE* or *para* genes, the combination of these references does not render the instant claims unpatentable since, as amended, the claims require the co-expression of isolated *tipE* and *para* genes.

The Loughney et al. reference is relied upon for a teaching of the isolated *para* locus of *Drosophila*, while Hall et al., is relied upon as a teaching of the an isolated cDNA that encodes the *tipE* gene.

In response, it is noted that while Loughney et al., disclose sequence data for an isolated *para* gene, Hall et al., disclose no sequence data. Accordingly, the Hall et al., reference is not an enabling disclosure for an isolated *tipE* gene. Under controlling legal precedent, in order for a reference to be available as a valid reference for purposes of anticipatory or obviousness rejections, the reference has to be enabling. See In re Bell, 991 F.2d 781 (Fed. Cir. 1993); In re LeGrice, 133 USPQ 365 (CCPA 1962); Beckman Instruments Inc. v. LKB Produkter AB, 13 USPQ2d 1301 (CAFC, 1989).

As the Hall et al. reference fails as an enabling disclosure of the *tipE* gene, the combination of references fails to present a valid *prima facie* case of obviousness of claims 20-23. Reconsideration and withdrawal of this ground for rejection is therefore respectfully requested.

C. CLAIMS 24-26:

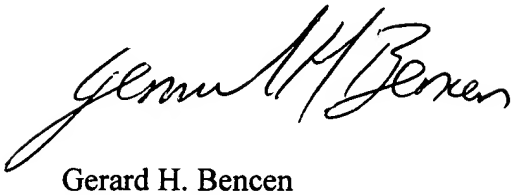
The Examiner has confirmed that claims 24-26 are free of the prior art. Accordingly, having addressed and overcome the stated grounds for rejection of these claims under 35 U.S.C. section 112, second paragraph, it is respectfully urged that claims 24-26 are in condition for allowance. Should the Examiner be of the opinion that any further amendment of these claims is required to place these claims in condition for allowance, it is respectfully requested that the Examiner telephonically contact the undersigned to discuss appropriate amendments to place these claims in allowable condition.

III. Conclusion:

In view of the foregoing amendments and remarks, it is respectfully urged that all grounds for objection or rejection have been addressed and overcome herein. Reconsideration and withdrawal of all grounds for objection and rejection is respectfully requested and rapid issuance of a Notice of Allowance in this case is respectfully solicited.

Should the Examiner find any basis on which it is believed that any of the claims as presented herein may be validly rejected, it is respectfully requested that the undersigned be contacted to discuss acceptable procedures for addressing any residual concerns that might delay issuance of a Notice of Allowance in this case.

Respectfully Submitted,



Gerard H. Bencen
Patent Attorney, Reg. No. 35,746
Gerard H. Bencen, P.A.
426 Anderson Court
Orlando, Florida 32801
Phone: 407-246-0444
Fax: 407-246-1879